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# A Literature Review of Concomitant Primary Biliary Cirrhosis and Graves' Disease

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## Abstract

Although Hashimoto's thyroiditis (HT) is commonly characterized by extrahepatic manifestations of primary biliary cirrhosis (PBC), coexistence of PBC and Graves' disease (GD) is uncommon. This is a review of the English and Japanese scientific literature, comprising 7 cases of PBC and GD coexistence. All patients were female. In 4 cases, both diseases were almost simultaneously diagnosed, whereas PBC preceded GD in the remaining 3 cases. One fatality was observed on account of sepsis and liver failure caused by progressing PBC.

**Keywords:** Primary biliary cirrhosis; Graves' disease; Basedow's disease; Autoimmune thyroid diseases; Hashimoto's thyroiditis

## Introduction

Primary biliary cirrhosis (PBC) is an autoimmune liver disease of unknown etiology, although the causes appear to involve environmental and genetic factors [1,2]. PBC is characterized by chronic progressive cholestasis with destruction of small intrahepatic bile ducts, particularly interlobular bile ducts [3-6].

On the other hand, autoimmune thyroid diseases include Graves' disease (GD) and Hashimoto's thyroiditis (HT). HT is one of the most common autoimmune endocrine diseases and is characterized by autoimmune-mediated destruction of the thyroid gland [7]. Although HT is commonly characterized by extrahepatic manifestations of PBC, coexistence of PBC and GD is uncommon. Moreover, it is unclear whether cases of concomitant PBC and GD occur incidentally or whether they share a common immunological basis.

To date, there have been few systematic literature reviews of concomitant PBC and GD. Here we performed a literature search and reviewed cases of concomitant PBC and GD.

## Methods

We reviewed the English and Japanese scientific literature on concomitant PBC and GD published since 1980 and summarized the findings of all relevant reports. The literature search was performed using the following keyword combinations: (1) primary biliary cirrhosis and Graves' disease (or Basedow's disease), (2) primary biliary cirrhosis and hyperthyroidism, and (3) primary biliary cirrhosis and thyrotoxicosis. The English and Japanese literature searches were performed using PubMed and Japana Centra Revuo Medicina (Igaku Chou Zasshi), respectively.

For case definition of concomitant PBC and GD, we excluded non-autoimmune causes of thyrotoxicosis, such as leakage of thyroid hormones or overproduction or release of thyroid hormones from adenomatous goiters. Moreover, cases in which the causes of hyperthyroidism or thyrotoxicosis were unclear, those that did not fulfill the diagnostic criteria for GD [8], and those [9-11] in which any presence of anti-thyroid stimulating hormone (TSH) receptor autoantibodies (TRAbs) was not mentioned despite fulfilling the diagnostic criteria for GD [8] were also excluded.

Moreover, patients with PBC [12,13] who had not undergone liver biopsy or for whom histological findings were not mentioned in the article despite fulfilling the diagnostic criteria for PBC [14] were excluded.

## PBC

PBC is considered an autoimmune disease characterized by chronic progressive cholestasis with destruction of small intrahepatic bile ducts, particularly interlobular bile ducts [3-6]. PBC affects middle-aged women (women in their fifth or sixth decade) more often than men (ratio of 9–10:1) [15,16].

The clinical features and natural history of PBC vary significantly from asymptomatic to progressive disease [14]. Jaundice, pruritus due to cholestasis, and general fatigue are typical symptoms in patients with PBC. However, up to 60% of patients may have no clinical symptoms. Histopathologically, PBC is diagnosed by florid bile duct lesions, such as chronic non-suppurative destructive cholangitis and epithelioid granuloma formation [14].

The diagnosis of PBC is established when 2 of the following 3 objective criteria are present [14]: (1) elevated serum alkaline phosphatase (ALP) levels, (2) presence of anti-mitochondrial antibodies (AMAs), which are useful for the serological diagnosis of PBC (90%–95% of patients with PBC are AMA-positive) [6], and (3) liver histology findings.

The prognosis of PBC is often dependent on the development of portal hypertension or cirrhosis, indicating liver failure. Disease progression can be significantly inhibited by treatment with ursodeoxycholic acid (UDCA) in some cases [14,17]; however, patients with end-stage liver failure require organ transplantation [16].

## GD (Basedow's disease)

GD, known as Basedow's disease in Europe, is the most common cause of hyperthyroidism [1,2], with an annual incidence of 14–21 cases per 100,000 individuals [8,18]. Individuals of any age can be affected; however, the disease is more common in middle-aged women (i.e., women in their fourth, fifth, or sixth decade) [18].

GD is caused by circulating TRAbs that mimic the action of TSH, thereby resulting in an increased synthesis and release of thyroid hormones [8,18]. GD is associated with extrathyroidal manifestations, including orbital disease (ophthalmopathy), skin changes, and rarely, fingertip and nail abnormalities [18].

The diagnostic criteria for GD include clinical and/or biochemical evidence of thyrotoxicosis and ≥1 of the following features: 1) presence of serum TRAbs, 2) ophthalmopathy and/or dermopathy, and 3) diffuse elevated thyroid radioiodine uptake [8].

## GD Complicated by PBC

Sjögren's syndrome (SjS) appears to be the most common autoimmune disorder that exists concomitantly with PBC [19-22]. Similarly, HT, rheumatoid arthritis (RA), systemic sclerosis (SS), and Raynaud's disease may coexist with PBC [21-23].

Silveria et al. [24] reported that among 67 patients with PBC, 32 (48%) had at least 1 extrahepatic autoimmune disease, and 9 (13.4%) had thyroid dysfunction. However, in that study, the incidence of GD in PBC patients was unknown. Few reports are available regarding the incidence of GD or hyperthyroidism in PBC patients. Recently, Floreani et al. [23] reported that among 361 patients with PBC who were followed up for 8 ± 6.9 years, 221 (61.2%) had at least 1 extrahepatic autoimmune disease. Furthermore, they found a significant positive association between the female sex and extrahepatic manifestations of autoimmune conditions in PBC; hence, there were no significant correlations among positive AMA, histological stage, and mean age at the time of PBC diagnosis with or without extrahepatic autoimmune conditions. They also reported that among 361 patients with PBC, 7 (1.9%) had GD and 45 (12.5%) had HT [23].

## Genetic factors associated with both PBC and GD

Some studies have assessed possible common genetic factors in PBC and GD patients. Human leukocyte antigen (HLA)-DRB1*08 alleles have been reported to be associated with the risk of both PBC and GD [25]. On the other hand, possible non-HLA genes such as protein tyrosine phosphatase non-receptor type 22 (PTPN22), cytotoxic T-lymphocyte antigen 4 (CTLA4), and CD40 may influence the risk of developing GD [26,27]. Although some studies have reported that the PTPN22 polymorphism C1858T is associated with GD, it has not been observed to influence the risk of PBC in previous studies [28,29]. However, some studies have suggested that polymorphism in exon 1 of the CTLA-4 gene at position 49 (+49A/G, rs231775) may influence the risk of GD [27,30] and also the risk of PBC [31-33]. Therefore, genetic factors such as CTLA-4 may be a candidate for a susceptibility locus driving concomitant cases of PBC and GD, although further investigations to identify common genetic factors in both PBC and GD are warranted.

To the best of our knowledge, these genetic factors have not been investigated or discussed in previously reported cases of concomitant PBC and GD. Therefore, it is uncertain whether some patients with concomitant PBC and GD have common genetic susceptibility and/or an immunological background favoring the development of these diseases.

## Characteristics of concomitant PBC and GD cases

The characteristics of the 7 reported cases of concomitant PBC and GD are summarized in Table 1 [25,34-39]. All patients were females. In 4 cases, PBC and GD were diagnosed simultaneously, whereas PBC was diagnosed before the development of GD in the remaining 3 cases. The concomitant disease was diagnosed at an age between 41 and 63 years. The interval between the diagnosis of the primary and concomitant diseases was 0–8 years, which is relatively short.

| Case | Year | Sex | Age at Diagnosis of PBC(Yrs) | Age at Diagnosis of GD (Yrs) | PBC prior to GD | Scheuers Classification | Complications | Remarks | References |
|---|---|---|---|---|---|---|---|---|---|
| 1 | (1994) | F | 52 | 52 | Sim | 1-3 | Mixed connective tissue disease | | [34] |
| 2 | (1999) | F | 54 | 54 | Sim | 4 | | Sepsis→death | [35] |
| 3 | (2000) | F | 55 | 55 | Sim | 3 | HTLV-1associated myelopathy | | [36] |
| 4 | (2005) | F | 41 | 41 | Sim | 1 | | | [37] |
| 5 | (2007) | F | 53 | 59 | + | 1 | Sjogreens syndrome, CREST syndrome | | [38] |
| 6 | (2007) | F | 54 | 57 | + | 3 | | Reversable janudice | [39] |
| 7 | (2013) | F | 55 | 63 | + | 4 | | | [25] |

**Table 1:** Characteristics of 7 Patients with comorbid primary biliary cirrhosis and Graves' disease.

Among concomitant cases, PBC at diagnosis varied in terms of stage (I–IV) according to Scheuer's classification. In concomitant cases of PBC and GD, other complicating autoimmune diseases were found in 2 cases: SjS and CREST syndrome in one case [38] and mixed connective tissue disease in the other case [34].

In 1 of the 7 cases, jaundice was attenuated along with normalization of thyrotoxicosis [39]. Although still unclear, a possible mechanism of jaundice progression or liver dysfunction after the onset of GD has been reported to be hypoxemia due to relatively decreased liver blood flow and increased oxygen consumption or circulatory disturbances that may be caused by high output heart failure or direct liver damage by thyroid hormone [39].

Standard pharmacotherapies for reported concomitant cases of PBC and GD include administration of UDCA and anti-thyroid drugs, such as thiamazole or propylthiouracil. Among the 7 cases, thiamazole-induced agranulocytosis occurred in 1 case, but the condition recovered after treatment [35]. Moreover, in 1 case, fatality occurred because of sepsis and liver failure due to PBC progression [35]. There was no fatality due to thyrotoxicosis itself.

## Conclusion

In this literature review, 7 cases of concomitant PBC and GD were seen to occur in females only. There were no cases of thyrotoxicosis-associated mortality; however, a fatality due to sepsis and liver failure was observed. At present, it remains uncertain whether these concomitant diseases occur incidentally or reflect a common immunological basis. Further studies are required to understand the pathophysiology and clinical features of concomitant PBC and GD cases.

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